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**Study ID:** 190342-038

**Title:** Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

**Protocol Amendment 7 Date:** 23-May-2017

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**Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in  
Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration  
(BEACON Study)**

Protocol Number: 190342-038 Amendment 7

EudraCT Number: 2013-003320-36

Phase: 2b

Name of Investigational Product: AGN-190342, Brimonidine Posterior Segment Drug Delivery System (Brimo DDS<sup>®</sup>)

Sponsor: Allergan (North America) Allergan Ltd.  
2525 Dupont Drive 1st Floor, Marlow  
Irvine, California USA International,  
92612 The Parkway, Marlow  
+1-714-246-4500 Buckinghamshire  
+1-800-347-4500 SL7 1YL United Kingdom  
Tel: +44 (0) 1628 494444  
Fax: +44 (0) 1628 494449

Emergency Telephone Numbers: Refer to the study contacts page in your investigator site file

Serious Adverse Event Reporting  
Fax Numbers: [REDACTED]

Serious Adverse Event Reporting  
Email Address: [REDACTED]

Allergan Medical Safety Physician  
Contact Information: [REDACTED]

Approval Date: 23-May-2017

Allergan Signatory:



Refer to the final page of this protocol for electronic signature and date of approval

The following information can be found on FDA Form 1572 and/or study contacts page:  
Name and contact information of Allergan study personnel; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; 21 CFR 312.23 section 6(iii)b.

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**INVESTIGATOR SIGNATURE PAGE**

INVESTIGATOR:

STUDY LOCATION:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

\_\_\_\_\_  
Investigator Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

Approval Date: 23-May-2017

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## Protocol Summary

**Study Compound:** AGN-190342, Brimonidine Posterior Segment Drug Delivery System (Brimo DDS®)

**Phase:** 2b

**Study Objectives:** to assess: (1) the safety of the treatment; (2) the effects of treatment on the mean change in atrophic lesion area quantified from fundus autofluorescence (FAF) images; (3) the effects of treatment on the mean change in low luminance best corrected visual acuity (BCVA); (4) the effects of treatment on the mean change in standard BCVA; (5) the effects of treatment on the mean change in retinal sensitivity quantified using scotopic/mesopic microperimetry; and (6) to characterize the systemic pharmacokinetic profile of Brimo DDS

**Clinical Hypotheses:**

- Brimo DDS is safe and well tolerated with repeated intravitreal administration in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) as assessed by the incidence of adverse events
- Brimo DDS is more effective than Sham treatment in slowing the growth of atrophic lesion area and the loss of standard and low luminance BCVA

**Study Design**

*Structure:* Multicenter, randomized, double-masked, Sham treatment-controlled study

*Duration:* 30 months

*Study Treatment Group:* 400 µg Brimo DDS administered by intravitreal injection

*Control:* Sham treatment with needleless DDS applicator

*Dosage/Dose Regimen:* One treatment to the study eye every 3 months from Baseline (Day 1) through Month 21

*Randomization/Stratification:* Randomization to treatment groups will use a 1:1 allocation ratio and will be stratified by region (North America, Europe, and Australia) and by atrophic lesion area ( $\leq 8 \text{ mm}^2$  versus  $> 8 \text{ mm}^2$ ) in the study eye as assessed by FAF examination at Screening Visit 1 and quantified by the central reading center (CRC).

**Study Population Characteristics**

*Number of Patients:* Approximately 300 (150 per treatment group)

*Condition/Disease:* GA secondary to age-related macular degeneration

*Key Inclusion Criteria:*

- Male or female patients 55 years of age or older

- [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - BCVA better than or equal to 45 letters (20/125 Snellen equivalent) at the Screening Visit 1 and the Baseline visit as assessed using the standard ETDRS (Early Treatment of Diabetic Retinopathy Study) visual acuity protocol
  - [REDACTED]
  - [REDACTED]
- The fellow eye must have standard BCVA of 34 letters (Snellen equivalent 20/200) or better at Screening Visit 1

*Key Exclusion Criteria:*

- [REDACTED]
- [REDACTED]
- [REDACTED]

**Response Measures**

*Efficacy:* Atrophic lesion area as assessed with FAF and quantified by the CRC; retinal sensitivity threshold as assessed with scotopic/mesopic microperimetry (selected sites/patients); standard BCVA as assessed with the ETDRS visual acuity protocol, and low luminance BCVA as assessed using 2.0 log unit neutral density filter and the ETDRS visual acuity protocol; [REDACTED]

[REDACTED]  
[REDACTED]  
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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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**General Statistical Methods and Types of Analyses:**

Analysis of safety data will be based on the safety population, ie, all patients who received at least one study treatment. Analysis of efficacy data will be based on the modified intent-to-treat population (mITT), ie, all randomized and treated patients with baseline and at least one post-baseline data point for atrophic lesion area. All analyses will be based on the actual treatment that the patient received.

The primary analysis for efficacy will be performed when all enrolled patients have completed the Month-24 visit or have exited early, prior to Month 24. An interim analysis may be performed after 50% of patients complete the Month-18 visit. Three database locks are planned for the study: an interim lock at Month 18 (50% of patients), the primary lock at Month 24, and the final lock at the end of the study (Month 30).

The primary efficacy variable is the change from Baseline in atrophic lesion area in the study eye as assessed with FAF and quantified by the CRC. Statistical analysis will be based on a mixed model for repeated measures (MMRM). The model includes treatment, study region (North America, Europe, and Australia), analysis visit, and treatment-by-visit interaction as factors as well as the baseline value and baseline value-by-analysis visit interaction as covariates.

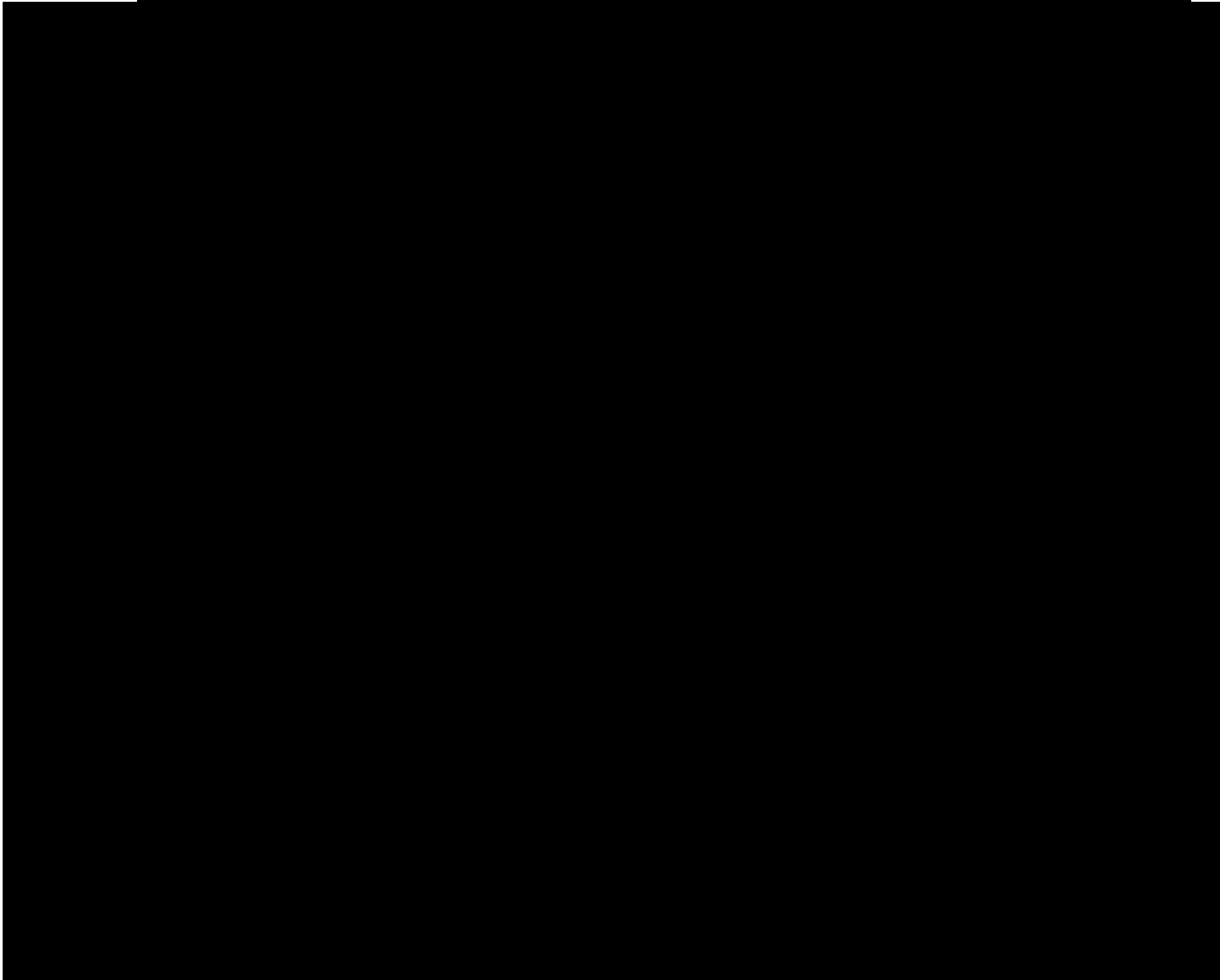
The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. The number and percent of patients reporting adverse events will be tabulated by primary system organ class, preferred term, and severity using the safety population.

***Sample Size Calculation:***

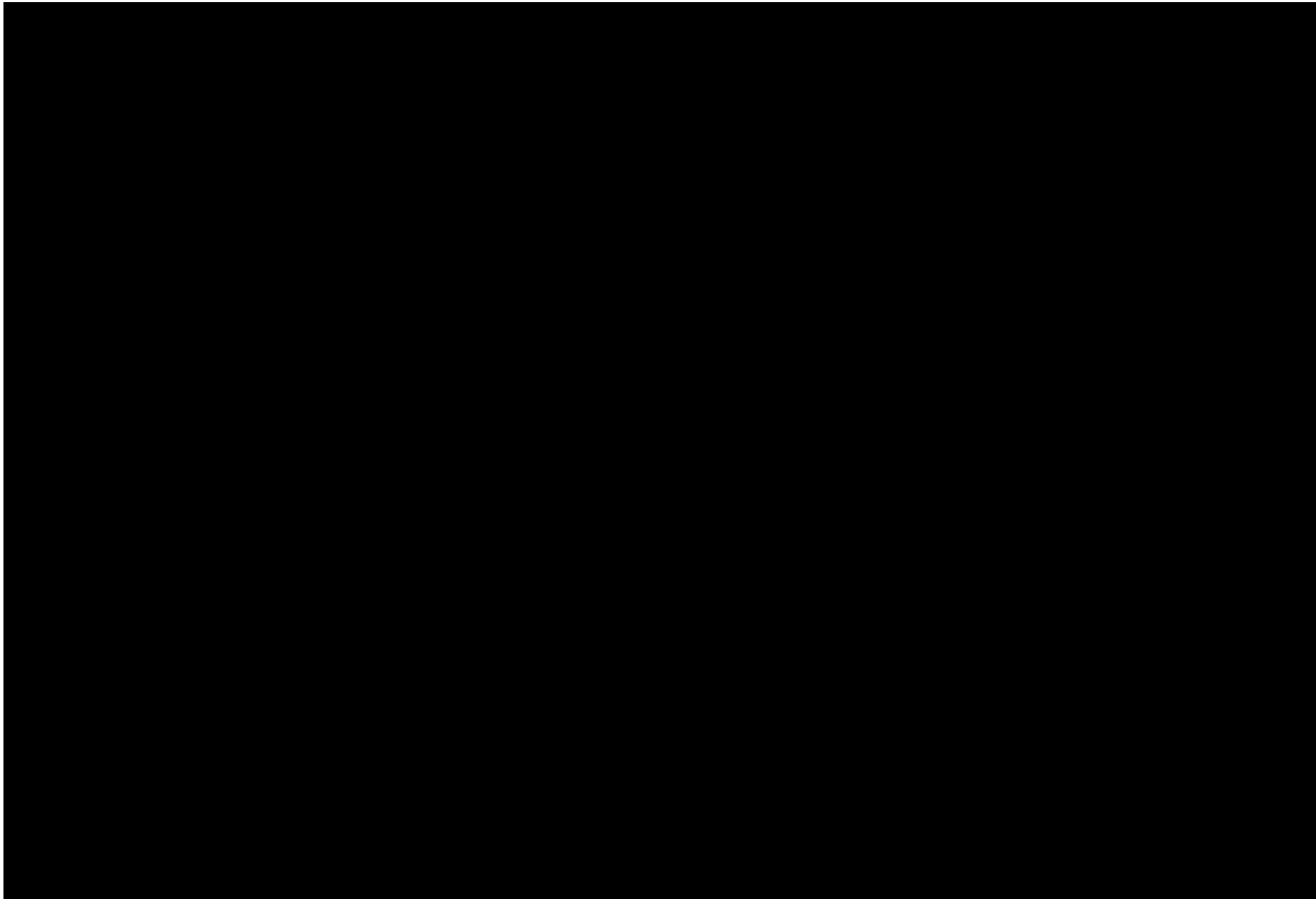
A standard method for measuring disease progression in patients with GA secondary to AMD is to quantify the expansion rate of the areas of atrophy. Over a 12-month period this expansion rate typically ranges between 1 and 2 mm<sup>2</sup> (Sunness et al, 2007; Holz et al, 2007; Holz et al, 2010). The atrophic lesion expansion rate used in the sample size calculation for the current study was from the GAP study (Holz et al, 2010). The selection of the GAP data was based on the large patient population in this natural history study and because of the similarities between the GAP study and the current study in both study design and patient populations.

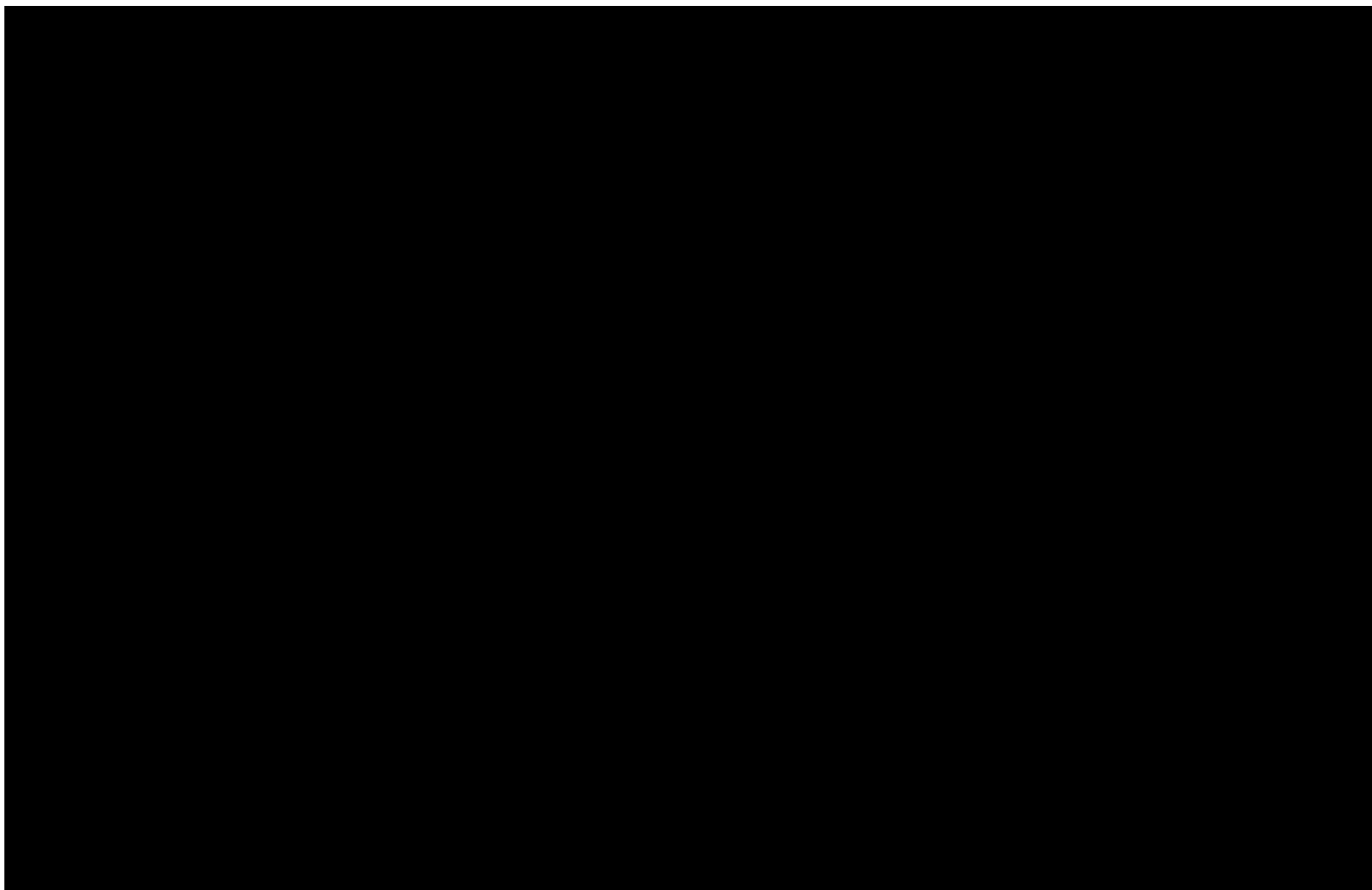
The 12-month lesion expansion rate from the GAP study was 1.73 mm<sup>2</sup>. A projected 24-month expansion rate, 2.8 mm<sup>2</sup>, was calculated by applying a 20% discount to a linear extrapolation of the GAP lesion expansion data. Based on this lesion expansion rate and assuming a common standard deviation of 1.65 mm<sup>2</sup>, a 2-sided t-test with 90% power and an alpha of 0.05 will require a sample size of 120 patients per group to detect a 25% reduction from the Sham treatment. A 25% reduction from the Sham treatment corresponds to a treatment

difference of 0.70 mm<sup>2</sup>. With an anticipated dropout rate of 20%, approximately 300 patients will be enrolled such that 240 (120 per group) will complete the Month 24 visit.



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## 1 Background and Clinical Rationale

Age-related macular degeneration (AMD) is the leading cause of legal blindness in persons over the age of 65 years (Friedman et al, 2004; Klein et al, 2006; Chakravarthy et al, 2007). Vision loss with this disease is attributed in large part to the advanced stages of this disease, exudative AMD and geographic atrophy (GA). While antibody fragments and antibody mimetics directed against vascular endothelial growth factor (VEGF) are effective treatments for exudative AMD (Rosenfeld et al, 2006; Brown et al, 2006; Heier et al, 2012), GA remains a large unmet medical need because of its high incidence and the absence of effective treatments. Klein and colleagues (2006) have reported that the 15 year cumulative incidence of GA in individuals 43 to 86 years old with early signs of AMD was 14%. In individuals over 85 years of age the incidence of GA is approximately 4 times that of exudative AMD (Klein et al, 2007).

GA is characterized by the degeneration of the retinal pigment epithelium (RPE), photoreceptor cells and choriocapillaris (Nowak, 2006). These morphological changes initially appear in the extrafoveal region and advance into the fovea as the disease progresses. In earlier stages when the disease is limited to the extrafoveal region, the atrophic lesions impair visual performance by limiting the size of the functioning fovea and patients may be able to see only a portion of words when reading. As the disease progresses to include the parafoveal region, central vision becomes affected. Severe vision loss occurs when these areas of atrophy enlarge or coalesce and expand into the foveola. In addition to the formation of scotomas that progress into the foveola, patients with geographic atrophy can experience a variety of visual symptoms such as distorted vision, trouble discerning colors, a slow recovery of visual function after exposure to bright light, a loss of contrast sensitivity and marked visual impairment in dimly lit environments (Sunness et al, 1997; Sunness et al, 2007; Sunness et al, 2008).

Previous studies have reported atrophic lesion expansion rates that range between 1.3 and 2.8 mm<sup>2</sup> per year (Klein et al, 2007; Age-Related Eye Disease Study [AREDS] Research Group, 2009; Holz et al, 2007; Fritsche et al, 2008; Sunness et al, 1999; Schatz and McDonald, 1989). While the majority of these studies have shown an association between the development of GA and systemic and environmental factors including blood pressure, smoking, heavy drinking status, body mass index, sedentary lifestyle, age, and gender, none of these studies have found an association between differences in intra-individual lesion expansion rates and systemic or environmental risks. In contrast to these findings, several natural history studies have identified a number of atrophic lesion characteristics that are associated with differences in lesion growth rates. In a 5-year



follow-up of 32 patients with GA, Klein and collaborators (2008b) reported that lesion growth is more rapid in lesions with multiple areas of atrophy, ie, multifocal lesions. Holz and colleagues have demonstrated that patterns of increased fundus autofluorescence (FAF) outside patches of GA also predict subsequent progression (Holz et al, 2007). In the Age Related Eye Disease study, baseline lesion area was an important predictor of subsequent lesion growth (AREDS Research Group, 2009). The GAP natural history study with baseline measurements from over 500 patients not only confirmed these associations between lesion phenotypic characteristics and lesion growth rates, but also reported that lesion growth is more rapid for extrafoveal lesions compared to foveal lesions (Holz et al, 2010). In the current study (BEACON Study) patients with unifocal atrophic lesions, lesions in which the total lesion area is greater than 18 mm<sup>2</sup> and lesions without perilesional hyperfluorescence will be excluded. The expectation is that this reduction in lesion phenotypic variability will decrease the variability of lesion growth rates, decreasing the sample size required to demonstrate a treatment effect in a study that is using atrophic lesion growth as the primary efficacy variable.

A number of genetic variants have been associated with both the neovascular and GA forms of advanced AMD. These include variants in complement factor H (CFH), complement factor B (CFB), complement factor 2 (C2), complement factor 3 (C3), apolipoprotein E and the age related maculopathy susceptibility 2 (ARMS2) locus (Gold et al, 2006; Yates et al, 2007; Seddon et al, 2007; Seddon et al, 2009). Of these CFH, C2, C3, CFB, and ARMS2 have been reported to predict the progression from intermediate to advanced AMD (Seddon et al, 2007; Francis et al, 2008). Together these findings prompted Scholl et al (2009) and Klein et al (2010) to assess whether specific alleles at these gene loci were associated with the rate of atrophic lesion growth. While these 2 studies confirmed the association of the high risk variants for CFH, C2, C3, and ARMS2 with the presence of GA, with the exception of ARMS2 in the study by Klein and colleagues (2010), there was no association between the high risk variants and atrophic lesion growth.

The association between genetic variants and treatment response has also been evaluated in several studies of advanced AMD. In a cohort of 397 patients the mean change in best corrected visual acuity (BCVA) following 3 intravitreal injections with ranibizumab was a 10-letter gain in patients homozygous for the non-risk genotype for CFH and ARMS2; in comparison, there was no improvement in BCVA in the group of patients homozygous for the CFH and ARMS2 high risk alleles (Smailhodzic et al, 2012). Similar findings have been reported in the ARED Study. In an analysis of a subgroup of category 3 and 4 patients, ie, those with the greatest risk for the development of advanced AMD, there was an association between treatment response and genetic risk factors. Within those patients homozygous for

the non-risk CFH allele, 34% treated with placebo versus 11% treated with anti-oxidants plus zinc progressed to advanced AMD. Within those patients homozygous for the high-risk CFH allele, 44% of the placebo-treated patients and 39% of the antioxidant-plus-zinc-treated patients progressed to advanced AMD (Klein et al, 2008a). In contrast to these findings, in the CATT (Comparison of AMD Treatments Trials) trial, which compared the treatment effects of ranibizumab and bevacizumab in 1185 patients with exudative AMD, there was no association between the genetic variants for CFH, C3 nor ARMS2 and the response to treatment (Hagstrom et al, 2013). More specifically, there were no high risk alleles that predicted final BCVA or change in BCVA, the degree of anatomical response nor the number of intravitreal injections.

In the BEACON study patients will be genotyped using a genome-wide array in an effort to uncover novel disease-associated genes. The variance of lesion growth explained by genotyped markers will be analyzed according to standard methods (Fritsche et al, 2016). A generally accepted genome-wide significance threshold will be adopted to determine if a variant (and thus a genetic locus) is significantly associated with GA lesion growth.

In nearly all of the epidemiological and natural history studies of GA, disease progression has been based on lesion growth assessments that were derived from color fundus photographs (Davis et al, 2005; Klein et al, 2008b; Schatz and McDonald, 1989; Sunness et al, 1997; Sunness et al, 1999; Sunness et al, 2007). With color fundus photography, lesion identification is based on an abrupt transition of fundus pigmentation which results from the atrophy of RPE cells. Due to inter-patient variability of fundus pigmentation, media opacities, the presence of drusen and small satellites of atrophy, graders at reading centers have commonly reported difficulty with reproducibly measuring atrophic areas from color fundus photographs (Pirbhai et al, 2005; Scholl et al, 2003; Sunness et al, 1999). An alternative approach for lesion area quantification, FAF imaging, has been used to quantify the progression of GA in a large multicenter study (Fundus Autofluorescence in Age-related Macular Degeneration [FAM] study) conducted in Germany (Bindewald et al, 2005; Holz et al, 2001; Holz et al, 2007; Schmitz-Valckenberg et al, 2006). With this technique imaging of atrophic lesions is based on the normal autofluorescence properties of RPE cells; the loss of RPE autofluorescence indicates disruption of the functional interaction between RPE and photoreceptor cells due to damage or death of photoreceptor cells and/or RPE cells (Schmitz-Valckenberg, 2009). While the loss of these cells is also visualized with color fundus photography, lesion boundary discrimination appears to be improved with FAF imaging (Sunness et al, 1999; Schmitz-Valckenberg, 2009; Schmitz-Valckenberg et al, 2011). Due to its increased boundary discrimination, FAF imaging will be used to evaluate the effect of brimonidine in the BEACON study.

Brimonidine (AGN-190342) is a selective alpha-2 adrenergic agonist with a long history of clinical use in the treatment of patients with ocular hypertension and open-angle glaucoma. Beyond its intraocular pressure (IOP)-lowering effect, brimonidine has also been reported to have cyto/neuroprotective effects (Evans et al, 2003; Tsai and Chang, 2005). It is postulated that the neuroprotective effect of brimonidine is mediated by activation of the alpha-2 adrenoceptor which is expressed throughout the neurosensory retina and is involved in pathways that inhibit apoptosis. In preliminary data from a rat model of retinal degeneration, systemic administration of brimonidine protected photoreceptors from photo-oxidative damage, as assessed with optical coherence tomography (OCT) and preserved photoreceptor function, as assessed with full-field electroretinography. The neuroprotective effects of brimonidine have also been observed in animal models of retinal vein occlusion, retinal ischemia and retinal detachment. Cytoprotective effects of brimonidine have been demonstrated in vitro, in human RPE (ARPE-19 cell line) and Müller cells (MIO-M1 cell line) (Ramírez et al, 2016). The use of brimonidine to preserve structural and functional capacity as demonstrated in animals may provide a novel mechanism for reducing the risk of retinal degeneration in human diseases such as geographic atrophy.

Brimonidine solution administered by intravitreal injection has a vitreal half-life of approximately 1.45 hours. Sustained retinal drug concentrations of brimonidine can be achieved when the drug is formulated into a solid implant composed of a biodegradable poly-D,L-lactide (PLA) and poly-D,L-lactide-co-glycolide polymer (PLGA) matrix and injected into the vitreous using the Novadur drug delivery system (DDS<sup>®</sup>). A formulation of this product using brimonidine tartrate salt (Brimonidine Tartrate Posterior Segment DDS or Brimonidine DDS [Generation 1]) has been used in animal studies and in clinical Phase 1 and Phase 2 studies.

In these human clinical studies Brimonidine DDS (Generation 1) (132 µg or 264 µg) was well tolerated (Studies 190342-028D, 190342-030D, 190342-031D, 190342-036, and 190342-032D). The majority of the treatment-related adverse effects were ocular and were attributed in large part to the injection procedure; the most frequently reported treatment-related adverse effects were conjunctival hemorrhage and conjunctival hyperemia.

Study 190342-032D investigated the use of Brimonidine DDS (Generation 1) (132 µg or 264 µg) compared with a Sham treatment in 117 patients with GA secondary to AMD; treatments with the sustained release formulation or Sham treatment were administered at the baseline visit and at the month 6 visit. In this study the safety profile was not different from that in clinical studies with a single injection. Three months after the first injection, the increase in atrophic lesion size was significantly smaller,  $p \leq 0.032$ , in both brimonidine-

treated groups compared with the Sham group; however, at the 12-month timepoint there were no between-group differences in lesion growth rates. The lack of statistical significance at the later timepoint may have been a consequence of the small sample size, the phenotypic heterogeneity of the patient population and/or the advanced stage of disease within the patient population. It is also conceivable that the dose and dosing frequency may have been insufficient to sustain an effective drug concentration in the retina.

To address this latter issue vitreous brimonidine levels were quantified over an 8-week time period in patients receiving 132 µg or 264 µg Brimonidine DDS (Generation 1) and then undergoing a pars plana vitrectomy (Study 190342-036). A pharmacokinetic model was then constructed based on these clinical data along with vitreous and retinal concentrations in monkeys treated with the Brimonidine DDS (Generation 1). Based on the pharmacokinetic model, retinal levels in man achieved with the Brimonidine DDS (Generation 1) were equivalent to those that preserved photoreceptor function in the acute model of photo-oxidative damage but only for 30 to 40 days after administration of the implant.

To support further studies in patients with GA, a new brimonidine sustained-release formulation has been developed (Brimonidine Posterior Segment Drug Delivery System [Brimonidine DDS (Generation 2)], hereafter called Brimo DDS). By changing the active ingredient from the tartrate salt to the free base, a 50% higher implant drug load can be achieved. Changing the PLGA/PLA polymer blend created a more rapid degradation of the polymer matrix, which achieves not only a more rapid release of brimonidine, but also higher retinal levels. With this new formulation, 4 months after administration of the 400-µg implant, macular concentrations of brimonidine in monkeys were 2-fold above the effective retina concentration in the acute photo-oxidative model. Pharmacokinetic/pharmacodynamic modeling suggests that dosing every 3 months will maintain brimonidine concentrations in the retina that are equivalent to the concentrations that protected photoreceptors in an acute photo-oxidative model of retinal degeneration.

In addition to the modified drug formulation, the size of the implants was modified to permit their delivery with a smaller needle, ie, a 25-gauge compared with a 22-gauge needle in the previous formulation. Using a smaller needle for implant delivery is expected to result in fewer injection-related adverse events, greater patient comfort, and a better product safety profile.

The cyto/neuroprotective effects of Brimonidine DDS (Generation 1) observed in animal studies, as well as the safety and effectiveness reported in human studies, suggest that brimonidine has the potential for slowing disease progression in patients with geographic

atrophy secondary to AMD. The improvements in the formulation and the reduction of inter-patient phenotypic variability, as well as the use of newer ocular imaging modalities, may allow better detection of an efficacy signal in this population. Atrophic lesion area will be measured using FAF and correlated with spectral-domain optical coherence tomography (SD-OCT). The combination of these imaging modalities will provide both quantitative and qualitative assessments of lesion progression. Structural measurements will be supplemented with assessment of photoreceptor function using microperimetry, facilitating correlations between functional and structural degeneration at precise areas of the retina. Genotypic analysis will be performed to provide a greater understanding of the relationship between specific genes variants and their association with GA progression and/or treatment benefit.

## **2 Study Objectives and Clinical Hypotheses**

### **2.1 Study Objectives**

The study objectives are to assess: (1) the safety of the treatment; (2) the effects of treatment on the mean change in atrophic lesion area quantified from FAF images; (3) the effects of treatment on the mean change in low luminance BCVA; (4) the effects of treatment on the mean change in standard BCVA; (5) the effects of treatment on the mean change in retinal sensitivity quantified using scotopic/mesopic microperimetry; and (6) to characterize the systemic pharmacokinetic profile of Brimo DDS.

### **2.2 Clinical Hypotheses**

The clinical hypotheses are that:

- Brimo DDS is safe and well tolerated with repeated intravitreal administration in patients with GA secondary to AMD as assessed by the incidence of adverse events
- Brimo DDS is more effective than Sham treatment in slowing the growth of atrophic lesion area and the loss of standard and low luminance BCVA

## **3 Study Design**

This is a multicenter, double-masked, randomized, Sham treatment-controlled, 30-month phase 2b study designed to evaluate the safety and efficacy of Brimo DDS in patients with GA secondary to AMD. Patients will be randomized in a 1:1 ratio to receive 400 µg Brimo DDS, administered by intravitreal injection, or Sham treatment (control). The study medication will be administered every 3 months from Baseline (Day 1) through Month 21. The primary efficacy measure, the mean change in atrophic lesion area as assessed with FAF will be assessed at Month 24. In addition to quantifying structural changes of the retina,

functional assessments will be performed using scotopic/mesopic microperimetry, as well as standard and low luminance BCVA. Total duration of the study for each patient is 30 months following randomization/treatment. [REDACTED]

For patients who do not participate in the microperimetry procedure or patients from sites not participating in the microperimetry procedure, there will be only 1 Screening visit, and therefore 13 visits over the study duration.

### **3.1 Data Review Committee**

A Data Review Committee (DRC) consisting of physicians and trained study personnel, in addition to ad hoc internal/external experts, will assess study treatment effects throughout the study; these assessments will include a review of unmasked safety data and biodegradation of the implant to determine the appropriateness of continuing dosing and enrollment. The composition and activities of the committee are described in the DRC charter, a separate document.

## **4 Study Population and Entry Criteria**

### **4.1 Number of Patients**

Approximately 300 patients (150 per treatment group) will be enrolled in the study at approximately 40 sites. Two hundred forty patients are expected to reach Month 24 for the primary endpoint assessment. The anticipated dropout rate is 20%.

### **4.2 Study Population Characteristics**

To avoid selection bias, the investigator should ensure that all persons who meet the following inclusion and exclusion criteria are offered enrollment in the study. To ensure that the study population will be representative of all eligible patients, no additional exclusions can be applied by the investigator. Selection of patients will exclude all considerations of race, occupation, socioeconomic status, and gender. If both eyes meet all of the inclusion/exclusion criteria, the eye with the worst standard BCVA will be selected as the study eye. If both eyes meet all of the inclusion/exclusion criteria and BCVA values are identical for both eyes, the right eye will be selected as the study eye.

### 4.3 Inclusion Criteria

The following are requirements for entry into the study:

**General Criteria:**

1. Male or female patients 55 years of age or older as assessed at Screening Visit 1

[Redacted text block]

**The Study Eye must have:**

[Redacted text block]

[Redacted text block] with fundus photography and/or SD-OCT at Screening Visit 1 and confirmed by the CRC

7. BCVA better than or equal to 45 letters (20/125 Snellen equivalent) at Screening Visit 1 and the Baseline visit as assessed using the standard ETDRS (Early Treatment of Diabetic Retinopathy Study) visual acuity protocol

[Redacted text block]

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For patients participating in microperimetry assessments:

[Redacted]

**The Fellow Eye must have:**

10. Standard BCVA of 34 letters (Snellen equivalent 20/200) or better at Screening Visit 1

**4.4 Exclusion Criteria**

The following are criteria for exclusion from participating in the study:

**General Criteria:**

[Redacted]

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[REDACTED]

**Ocular Exclusion Criteria:**

[REDACTED]

- 10. History or evidence of the following surgeries/procedures in the study eye as assessed at Screening Visit 1, including:
  - a. Submacular surgery or other intervention for AMD
  - b. Vitrectomy
  - c. Intraocular retinal laser treatments within the last 3 months prior to Screening Visit 1
  - d. Incisional glaucoma surgery
  - e. Cataract surgery or laser-assisted in situ keratomileusis (LASIK) within the last 3 months prior to Screening Visit 1
- 11. Periocular or ocular/intraocular infection or inflammation in either eye (such as: infectious conjunctivitis, keratitis, scleritis, endophthalmitis) within the 3 months prior to Screening Visit 1

[REDACTED]

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## 4.5 Permissible and Prohibited Medications/Treatments


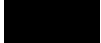
### 4.5.1 Permissible Medications/Treatments

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. All medications and procedures should be recorded in the electronic case report form (eCRF). If the permissibility of a specific medication/treatment is in question, please contact Allergan.

Use of the following medications is permissible during the study:

- Alpha-1 antagonists (eg, prazosin, terazosin, doxazosin, labetalol) and other selective alpha-antagonists that do not inhibit alpha-2 adrenoceptors
- Non-ocular use of alpha-2 agonists and alpha-2 antagonists are permissible if used for at least 30 days prior to Baseline, and the use of the medication is expected to remain stable (dose and dosing regimen) for the duration of the study. Any changes to such medications should be documented on the appropriate eCRFs.

YAG capsulotomy is recommended to be scheduled no sooner than 2 to 3 weeks before a scheduled Brimo DDS injection, or at least 2 to 3 weeks after a Brimo DDS injection. The YAG opening should be kept slightly smaller than the periphery of the IOL optic to reduce the chance that the Brimo DDS implants will migrate from the vitreous cavity to the anterior chamber.

In case of retinal tear, withhold the study treatment until the tear is successfully treated and resolved. Treatment may be re-initiated later at the investigator's discretion and if the patient does not meet any of the discontinuation criteria in Section   


If a patient develops choroidal neovascularization in the fellow eye, study treatment can continue in the study eye. The fellow eye should be treated according to best medical practice.

If cataract surgery is necessary, attempt to schedule cataract surgery  $\geq 7$  days after the most recent study treatment. Study treatment may be resumed  $\geq 14$  days after cataract surgery, assuming no surgery-related complications.

#### **4.5.2 Definition of Females of (Non-) Childbearing Potential and Acceptable Contraceptive Methods**

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (ie, hysterectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause. For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), vasectomized partner, or sexual abstinence.

The investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study.

If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with an investigational drug (Brimo DDS or Sham) and (2) follow the progress of the pregnancy. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

#### **4.5.3 Prohibited Medications/Treatments**

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered. Use of the following medications is prohibited during the study:

- Any periocular injection or intravitreally injected therapy
- Ocular use (other than the study medication) of brimonidine, apraclonidine, oxymetazoline, naphazoline, tetrahydrozoline, or any other medications with known alpha-2 agonist activity
- Inconsistent or intermittent use of systemic medications with known alpha-2 antagonism (eg, phentolamine, phenoxybenzamine, yohimbine, risperidone) or medications with known alpha-2 agonism (eg, methyldopa, clonidine, guanfacine, tizanidine)
- Use of roflumilast (Daliresp<sup>®</sup>) or other oral phosphodiesterase-4 inhibitors

#### 4.5.4 Escape Medications

There are no escape medications for this study.

#### 4.5.5 Special Diet or Activities

Patients are not required to fast prior to blood and urine collections for laboratory tests.

### 5 Study Treatments

#### 5.1 Study Treatments and Formulations

Brimonidine DDS Applicator System contains implant dosage of 400 µg [REDACTED]  
[REDACTED] in a PLA/PLGA biodegradable polymer matrix.

[REDACTED]

[REDACTED]

[REDACTED]

#### 5.2 Control Treatment

The Sham treatment will consist of a needleless DDS Applicator without study medication and is provided as a sterile finished product.

#### 5.3 Methods for Masking

The following individuals at the site will be masked to the study treatment for the duration of the study:

- Patients
- Assessing investigator(s) who performs ocular assessments (excluding post-injection assessment and DDS assessment)
- Study technicians, ie, individuals administering the following study assessments: microperimetry, standard BCVA, low luminance BCVA, FAF (standard and quantitative), IR, and SD-OCT

These masked technicians must not perform unmasking procedures such as fundus photography. They must not be present during the study treatment procedure, implant assessments, implant photography, or post-injection assessments and they must not complete case report forms (CRFs) or have access to other study data.

Masked study site staff members who become aware of the study treatment of an individual patient shall not continue to collect efficacy variables (excluding patient-reported outcomes [PROs]) for that patient.

[REDACTED]

CRC staff will be masked to the study treatment for the duration of the study.

Sponsor personnel masking, including handling of the interim analysis, is detailed in the Sponsor Masking Plan.

#### **5.4 Treatment Allocation Ratio and Stratification**

Patients will be randomized to treatment groups (Brimo DDS or Sham) in a 1:1 allocation ratio. Randomization will be stratified by region (North America, Europe, and Australia) and by atrophic lesion area ( $\leq 8 \text{ mm}^2$  versus  $> 8 \text{ mm}^2$ ) in the study eye as assessed by FAF examination at Screening Visit 1 and quantified by the CRC.

#### **5.5 Method for Assignment to Treatment Groups/Randomization**

Prior to initiation of study treatment, each patient who provides informed consent will be assigned a patient study number that will serve as the identification number on all study documents.

An automated interactive voice response system/interactive web response system (IVRS/IWRS) will be used to manage the randomization and treatment assignment based on a randomization scheme prepared by Allergan Biostatistics.

Study medication will be labeled with medication kit numbers. The IVRS/IWRS will provide the site with the specific medication kit number(s) for each randomized patient at the time of randomization. Sites will dispense study medication according to the IVRS/IWRS instructions. Sites will also call the IVRS or log onto the IWRS at subsequent visits to obtain a study medication kit number for dispensing study medication. Sites will receive the IVRS/IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

At the time of randomization at Baseline, eligible patients will be randomly assigned to either 400 µg Brimo DDS or Sham treatment.

## 5.6 Treatment Regimen and Dosing

Patients who are eligible for the study and have been randomized to receive active treatment, 400 µg Brimo DDS, will receive treatment during the Baseline visit of the study. [REDACTED]

Patients who are eligible for the study and have been randomized to the Sham treatment will receive the Sham treatment during the Baseline visit of the study. [REDACTED]

## 5.7 Storage of Study Medications/Treatments

The study medication must be stored in a secure area and administered at no cost to the patient and only to patients entered into the clinical study. Administration must be in accordance with the conditions specified in this protocol.

The Brimo DDS Applicator System must be stored at controlled room temperature in the original sealed foil pouch; temperature will be monitored by the sites. Exposure to excessive light and heat should be avoided. Please see the Procedure Manual for further instructions.

## 5.8 Preparation of Study Medications/Treatments

Prior to study treatment, the study eye of each patient will be anesthetized with topical anesthetic and prepared according to the standard protocol detailed in the Procedure Manual. The preparation of the patient for treatment (injection) and Sham procedures will be identical. Refer to the Procedure Manual for the detailed instructions.

## 5.9 Treatment Administration

Brimo DDS 400 µg will be administered by intravitreal injection in the study eye. The implant will be injected into the vitreous of the study eye through the pars plana. Refer to the Procedure Manual for the detailed instructions.

The Sham treatment is administered using a needleless DDS Applicator. Refer to the Procedure Manual for the detailed instructions.

## **6 Response Measures and Summary of Data Collection Methods**

### **6.1 Efficacy Measures**

#### **6.1.1 Primary Efficacy Measure**

- Atrophic lesion area in the study eye as assessed with FAF and quantified by the CRC

#### **6.1.2 Secondary Efficacy Measures**

- Low luminance BCVA of the study eye as assessed using a 2.0 log unit neutral density filter and the ETDRS visual acuity protocol
- Standard BCVA of the study eye assessed using the ETDRS visual acuity protocol

#### **6.1.3 Other Outcome Measures**

In addition to the primary and secondary efficacy measurements, the following outcomes will be measured in the study eye:

- Retinal sensitivity threshold as assessed with scotopic/mesopic microperimetry

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## 6.4 Examination Procedures, Tests, Equipment, and Techniques

Additional details about the procedures may be found in the Procedure Manual.

### 6.4.1 Certification of Technicians and Examiners

To enhance standardization and quality, technicians performing dilated fundus photography, fluorescein angiography, FAF (standard and quantitative), near-IR, SD-OCT, and

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scotopic/mesopic microperimetry will be certified. Certification by the CRC of the equipment and examiners at each investigative site will occur prior to patient screening.

#### **6.4.2 Standard and Low Luminance Best Corrected Visual Acuity**

Standard BCVA will be quantified using the ETDRS visual acuity protocol. BCVA testing should precede any examination requiring contact with the eye. BCVA should be performed following manifest refraction. Low luminance BCVA will be measured using 2.0 log unit neutral density filter and the ETDRS visual acuity protocol. Certification and procedures for performing the standard and low luminance BCVA measurements are included in the Procedure Manual.

#### **6.4.3 Spectral-domain Optical Coherence Tomography**

SD-OCT images collected in the study may be collected only with the [REDACTED]. [REDACTED] A standardized procedure for obtaining SD-OCT images using [REDACTED] is included in the Procedure Manual. SD-OCT images from each of the specified study visit will be sent to the CRC; images from the Screening Visit 1 will be used to define foveal involvement and patient eligibility as confirmed by the CRC.

#### **6.4.4 Microperimetry**

Scotopic/mesopic microperimetry will be performed at selected sites. Patients at these sites can enroll into the study if they decline to participate in the scotopic/mesopic microperimetry assessments, or if they do not meet inclusion criterion #9 (Section 4.3). Scotopic/mesopic microperimetry assessments may only be performed with the Nidek MP-1 Scotopic (MP-1S) microperimeter. A customized procedure for microperimetry using the Nidek MP-1S is included in the Procedure Manual. Nidek MP-1S images will be sent to the CRC.

The reproducibility of the mean retinal sensitivity threshold measurements from the repeat assessment performed during the Screening Visit 2 will be used to evaluate patient eligibility for the microperimetry procedure, as confirmed by the CRC. The Nidek MP-1S image-assessment report from each visit, beginning with the Baseline visit, will be submitted to the CRC; these reports will include the fundus images submitted in an uncompressed format.

#### **6.4.5 Confocal Scanning Laser Ophthalmoscopy: Near-infrared Reflectance (3-field)**

A standardized procedure for obtaining near-IR images using the [REDACTED] is included in the Procedure Manual. Three-field images collected at the specified visits will be sent to the CRC.

#### **6.4.6 Confocal Scanning Laser Ophthalmoscopy: Quantitative (Central Field) and Standard (3-field) Fundus Autofluorescence**

A standardized procedure for obtaining FAF images using the confocal scanning laser ophthalmoscopy (cSLO) capability of the [REDACTED] is included in the Procedure Manual.

In addition to the standard FAF imaging, quantitative FAF images will be obtained in the study eye at the specified study visits (as per [Table 1](#)) for assessing changes in autofluorescence intensity mapping/retinal sensitivity in patients who participate in the microperimetry procedure. Both the standard FAF and quantitative FAF images will be sent to the CRC. The standard FAF images from Screening Visit 1 will be used by the CRC to assess patient eligibility.

#### **6.4.7 Fluorescein Angiography**

Fluorescein angiographic imaging should be performed with the [REDACTED]; if this system is not available investigators may collect these images with a standard fundus camera based system (the minimum requirements for settings are described in the Procedure Manual). Images collected at the Screening Visit 1 will be used by the CRC to confirm patient eligibility. Images from the Screening Visit 1 and the Exit visit will be sent to the CRC. Fluorescein angiography may be performed at any visit if needed to confirm development of choroidal neovascularization.

#### **6.4.8 Indocyanine Green Angiography (Optional)**

Indocyanine green (ICG) angiography may be performed during Screening Visit 1 if it is considered necessary to exclude patients with late-onset Stargardt disease. A standardized procedure for the collection of ICG angiograms from both eyes is included in the Procedure Manual. [REDACTED] should be used to collect the images; if this system is not available, investigator may collect these images with a standard fundus

camera based system (the minimum requirements for settings are described in the Procedure Manual). Images may be collected at the Screening Visit 1 if the investigator suspects late-onset Stargardt disease. If ICG is performed, the images will be sent to the CRC to confirm patient eligibility.

### 6.4.9 Dilated Fundus Photography

Dilated fundus photographic images (fundus reflex, 3-field color imaging, and central field red-free photographs) will be collected from both eyes at the Screening Visit 1 and the Exit visit. These fundus images will be kept at the site and copies will be sent to the CRC. The images collected at the Screening Visit 1 will be used by the CRC to confirm patient eligibility.

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## 6.5 Other Study Supplies

Allergan will make provisions (directly or indirectly) to supply the study sites with pregnancy test kits; ETDRS instrumentation (if needed); medications or supplies (eg, anti-infective ophthalmic solution, local anesthetic eye drop, dilating eye drop, povidone iodine, syringe, needles, cotton tip swabs, cellulose sponges), and blood sampling kits for pharmacokinetic analysis (at selected sites), genotyping, and gene expression. Tubes for collection of samples for clinical laboratory analysis will be provided by a central laboratory.

## 6.6 Summary of Methods of Data Collection

Clinical data for this study will be collected in eCRFs using the Phase Forward Inform System. Data entered into the eCRF will correspond to and be supported by source documentation maintained at the site. Data will be transferred to Allergan from the CRC and genotyping laboratory.

## 7 Statistical Procedures

The primary analysis for efficacy will be based on data collected through Month 24. An interim analysis may be performed after 50% of patients complete the Month 18 visit. Up to 3 database locks are planned for the study: an interim lock at Month 18 (50% of patients), the primary lock at Month 24, and the final lock at the end of the study (Month 30).

Statistical methods for data analyses will be detailed in the analysis plan as a separate document which will be finalized prior to the first interim lock.

### 7.1 Analysis Populations

The following 2 populations will be used for statistical analyses: modified intent-to-treat (mITT) and safety.

The mITT population will include all randomized and treated patients with Baseline and at least one post-baseline measurement for the atrophic lesion area. The mITT population will be used for analyses of efficacy variables. The safety population will include all treated patients and will be used for safety analyses. All analyses will be performed based on the randomized treatment.



## **7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments**

The primary efficacy measure in this study is the atrophic lesion area measured by FAF examination. The primary timepoint for the efficacy analysis is Month 24.

### **7.2.1 Primary Efficacy Variable**

The primary efficacy variable is the change from Baseline in the atrophic lesion area in the study eye, assessed with FAF and quantified by the CRC.

### **7.2.2 Secondary Efficacy Variables**

The secondary efficacy variables are (1) change from Baseline in low luminance BCVA in the study eye as assessed using a 2.0 log unit neutral density filter and the ETDRS visual acuity protocol (2) change from Baseline in standard BCVA in the study eye as assessed with the ETDRS visual acuity protocol.

## **7.3 Hypothesis and Methods of Analysis**

### **7.3.1 Primary Efficacy Analyses**

The primary efficacy variable is the change from Baseline in atrophic lesion area in the study eye. The primary analysis will use the mITT population and will be based on a mixed model for repeated measures (MMRM) that includes treatment, study region (North America, Europe, and Australia), analysis visit, and treatment-by-visit interaction as factors as well as the baseline value and baseline value-by-analysis visit interaction as covariates. The least-squares means (LS means) for change from baseline will be calculated for each group. Statistical test for the between-group difference (Brimo DDS versus Sham) in LS means and the construction of the corresponding 2-sided 95% confidence intervals will be done using the same MMRM model. If warranted, data transformation will be applied to the effective diameter (ED) (such as the square root transformation), and the final statistical analysis for the change from baseline will be based on the transformed data.

### **7.3.2 Secondary Efficacy Analyses**

Analysis of data collected for both standard and low luminance BCVA will include change from baseline in BCVA scores as the number of letters read correctly and categorical change in BCVA.

Analyses will be performed using the mITT population. MMRM that includes treatment, study region (North America, Europe, and Australia), analysis visit, and treatment-by-visit interaction as factors as well as the baseline value and baseline value-by-analysis visit interaction as covariates will be applied. The LS means for change from baseline will be calculated for each group. Statistical test for the between-group difference (Brimo DDS versus Sham) in LS means and the construction of the corresponding 2-sided 95% confidence intervals will be done using the same MMRM model.

[REDACTED]

### 7.3.4 Safety Analyses

Statistical analysis for safety will be based on the safety population. The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events and biomicroscopy and ophthalmoscopy data. The number and percent of patients reporting adverse events will be tabulated by primary system organ class, preferred term, and severity. The summary tables will be generated separately for adverse events reported during the screening to baseline period (pre-treatment adverse events) and treatment period (treatment-emergent adverse events [TEAEs]). Summaries for TEAEs will be organized into the following: all adverse events regardless of causality; treatment-related adverse events; ocular adverse events in the study eye; treatment-related ocular adverse events in the study eye; and primary safety measures as outlined in Section 6.3. Group comparisons will be done using a chi-square test or Fisher’s exact test as appropriate.

[REDACTED]

### 7.4 Subgroup Analyses

Analyses of subgroups defined by important baseline disease characteristics (such as lesion size), will be performed, if applicable.

### 7.5 Sample Size Calculation

A standard method for measuring disease progression in patients with GA secondary to AMD is to quantify the expansion rate of the areas of atrophy. Over a 12-month period this expansion rate typically ranges between 1 and 2 mm<sup>2</sup> (Sunness et al, 2007; Holz et al, 2007; Holz et al, 2010). The atrophic lesion expansion rate used in the sample size calculation for the current study was from the GAP study (Holz et al, 2010). The selection of the GAP data was based on the large patient population in this natural history study and because of the similarities between the GAP study and the current study in both study design and patient populations.

The 12-month lesion expansion rate from the GAP study was 1.73 mm<sup>2</sup>. A projected 24-month expansion rate, 2.8 mm<sup>2</sup>, was calculated by applying a 20% discount to a linear extrapolation of the GAP lesion expansion data. Based on this lesion expansion rate and assuming a common standard deviation of 1.65 mm<sup>2</sup>, a 2-sided t-test with 90% power and an alpha of 0.05 will require a sample size of 120 patients per group to detect a 25% reduction from the Sham treatment. A 25% reduction from the Sham treatment corresponds to a treatment difference of 0.70 mm<sup>2</sup>. With an anticipated dropout rate of 20%, approximately 300 patients will be enrolled such that 240 (120 per group) will complete the Month 24 visit.

The sample size calculations are based on the procedure MTTO-1 in nQuery (v6.01).

### 7.6 Interim Analyses

An interim analysis may be performed after 50% of patients have completed the Month 18 visit or have exited early from the study. To maintain an overall Type I error rate at 0.05 level, the significance level will be 0.001 for the interim analysis at Month 18 and 0.05 (Haybittle–Peto method) for the Month 24 analysis. The purpose of the interim analysis is to support the decision making process and the planning of further development.

To maintain the integrity of the study, individuals who are directly involved in study conduct and data management will remain masked to treatment assignment of individual patients until study completion.

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## **8.1 Patient Entry Procedures**

### **8.1.1 Overview of Entry Procedures**

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

### **8.1.2 Informed Consent and Patient Privacy**

The study will be discussed with the patient and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization (US only), data protection consent (Europe only), and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each patient who provides informed consent will be assigned a patient number that will be used on patient documentation throughout the study.

## **8.2 Procedures for Final Study Entry**

Patient eligibility based on lesion characteristics, as well as the reproducibility of the retinal sensitivity measurements, must be confirmed by the CRC prior to patient randomization. Patients at sites participating in scotopic/mesopic microperimetry can enroll into the study if they decline to participate in the microperimetry procedure , or if they do not meet inclusion criterion #9 (Section 4.3). In addition, all screening laboratory tests must be performed, and the results must be evaluated and determined to be acceptable to the investigator prior to patient randomization into the study. Screening laboratory tests may be repeated once at the discretion of the investigator or Allergan.

Female patients of childbearing potential must have a negative pregnancy test result prior to entry into the study.

A patient is considered to have entered the study at the time of randomization to treatment on Day 1. See Section 5.5 for the method for assignment to treatment groups/randomization.

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**8.4 Instructions for the Patients**

If a site dispenses pre- and/or post-injection anti-infectives, at the time the anti-infectives are dispensed, the patient should be instructed when and how to use them.

**8.5 Unscheduled Visits**

Additional examinations may be performed as necessary to ensure the safety and wellbeing of patients during the study. The eCRF should be completed for each unscheduled visit.

**8.6 Compliance With Protocol**

Allergan must be informed of any patients who are inadvertently enrolled despite significant deviation from protocol-specified criteria. A decision regarding the patient’s continued participation will be made on a case-by-case basis.

**8.7 Early Discontinuation of Patients**

Patients may voluntarily withdraw from the study at any time. The investigator may stop the patient’s participation at any time. Notification of patient discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate CRF.

Patients who develop neovascular AMD must be discontinued. Any patient who develops a concomitant retinal disorder in the study eye that prevents retinal visualization and quantification of the area of atrophic lesions, or causes a sustained  $\geq 30$  letter loss of BCVA (a sustained loss is defined as a loss evident on 2 consecutive study visits) must be discontinued.

For patients who discontinue from the study early, every effort should be made to have these patients return to the clinical center for completion of the exit visit. Additionally, patients who discontinue from the study early should be encouraged to return to the clinical center for an ophthalmological evaluation 12 weeks after their most recent study treatment. Adverse events leading to patient early discontinuation must be followed-up as appropriate.

### 8.7.1 Treatment Failures

Allergan considers the benefit-risk of study participation to be positive, and does not recommend study discontinuation due to treatment failure. Currently, there are no approved treatments for GA, and consequently there are no standard-of-care treatment options available for patients who fail study treatments. Further, inclusion of treatment failure criteria in a masked study may introduce bias. As an example, treatment failure criteria based on lesion progression may apply unequally by treatment assignment (Sham versus active), where potentially more Sham-treated patients would be identified as treatment failures. Likewise, removal of patients who fail active treatment would also create a bias towards the appearance of more significant study drug effects.

Results from clinical studies to date suggest a positive benefit-risk profile of the study treatment. The Phase 2a clinical study 190342-032D results in patients with GA suggest a modest effect of Brimo DDS. In the 190342-032D study, patients treated with Brimo DDS (Generation 1) 264  $\mu\text{g}$  experienced a 27.4% reduction in GA progression rate at the 12-month primary timepoint compared with sham-treated patients. Exploratory analysis of these data ([Kupfermann et al, 2017](#)) indicates that the effects of Brimo DDS may be even larger in a subpopulation of fast-progressing patients (defined as patients with baseline GA  $\geq 9 \text{ mm}^2$ ). Reductions in progression rate in this subpopulation were nearly 38% and this effect was statistically significant. As a progressive disease, continuation of treatment may be necessary to realize a clinically meaningful outcome on disease progression. Clinical study safety results to date, including a long-term safety study, suggest that Brimo DDS is well tolerated, and risks associated with the study treatment are mainly related to the intravitreal injection. Likewise, patients randomized to Sham have no increased risk with additional Sham treatments, as these are needleless. Given these considerations, Allergan considers the

preponderance of evidence to favor study participation, as compared with absence of treatment. Therefore, criteria for treatment failure are not included in this protocol.

## **8.8 Study Termination**

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

## **9 Adverse Events**

Adverse events occurring during the study will be recorded on an adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

### **9.1 Definitions**

#### **9.1.1 Adverse Event**

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Progression of the treatment indication, including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should not be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as “How have you been feeling since the last visit?” Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate CRF.



### 9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization are not reportable as serious adverse events.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

### 9.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an "all or nothing" finding which cannot be graded.

### 9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a

determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

Note: a study procedure occurring during the screening/baseline period can include a washout of medication or introduction of a run-in medication or study required diagnostic procedure.

For treatment-related adverse events, the investigator will note on the eCRF whether the event is related to the study drug (DDS) and/or the applicator, and/or the insertion procedure.

## **9.2 Procedures for Reporting Adverse Events**

Any adverse event must be recorded on the appropriate CRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked "ongoing" at the exit visit must be followed-up as appropriate.

## **9.3 Procedures for Reporting a Serious Adverse Event**

Any serious adverse event occurring during the study period (beginning with informed consent) and any serious ocular adverse event occurring within 4 months after the last dose of study treatment must be immediately reported but no later than 24 hours after learning of a serious adverse event.

Serious adverse events must be reported to Allergan as listed on the Allergan Study Contacts Page and recorded on the serious adverse event form. All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form; phone numbers and relevant Allergan personnel contacts are also on the front page of protocol).
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanations for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

#### **9.4 Procedures for Unmasking of Study Medication**

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the Allergan Medical Safety Physician should be notified prior to unmasking study medication. The investigator should inform the Allergan Medical Safety Physician of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the patient can be determined by designated site personnel calling into the IVRS or IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

### **10 Administrative Items**

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

#### **10.1 Protection of Human Patients**

##### **10.1.1 Compliance With Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations**

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative. If the patient is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

### **10.1.2 Compliance With IRB or IEC Regulations**

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

### **10.1.3 Compliance With Good Clinical Practice**

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

### **10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)**

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

## **10.2 Changes to the Protocol**

The investigator must not implement any deviation from or changes to the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

## **10.3 Patient Confidentiality**

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the sponsor of the study, Allergan, or the governing health authorities or the Food and Drug Administration if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

### **10.3.1 Patient Privacy**

Written authorization (US sites only), data protection consent (European sites only), and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each patient prior to enrollment into the study. These authorizations are to be obtained from each patient and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act ("HIPAA") Standards for Privacy of Individually Identifiable Health Information, EU Data Protection Directive 95/46/EC ["EU Directive"]).

In accordance with HIPAA requirements, additional purposes of this study include the following: to publish anonymous patient data from the study; and to create and maintain a data repository.

## **10.4 Documentation**

### **10.4.1 Source Documents**

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the CRFs serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record and/or maintained as source documents:

- Patient's name
- Patient's contact information
- The date that the patient entered the study, patient number, and patient randomization (or medication kit) number
- The study title and/or the protocol number of the study and the name of Allergan
- A statement that informed consent was obtained (including the date); a statement that written authorization (US sites only), data protection consent (EU sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date)
- Dates of all patient visits
- Medical history and ophthalmic history

- All concurrent medications (list all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Visual acuity worksheets (standard BCVA and low luminance BCVA)
- Results of abnormal findings from complete ophthalmic examination (including external examination of the eye and adnexa, screening for eyelid/pupil responsiveness, slit-lamp biomicroscopy, indirect ophthalmoscopy, dilated fundus examination, and IOP)
- Occurrence and status of any adverse events
- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- Copies of the laboratory reports generated by the central laboratory for the analysis of blood and urine samples
- SD-OCT electronic files (including back-up files)
- Nidek MP-1S microperimetry electronic files (including back-up files)
- cSLO 3-field near-IR electronic files (including back-up files)
- cSLO 3-field FAF electronic files (including back-up files)
- cSLO central field qFAF electronic files (including back-up files)
- Fluorescein angiography electronic files (including back-up files)
- Dilated fundus photography (fundus reflex, 3-field color imaging, central field red-free photograph) electronic files (including back-up files)
- ICG angiography (if ICG is performed) files (including back-up files)
- Procedure notes of the study treatment procedure should include the following:
  - date and time of the procedure
  - evaluation of the injection site
  - location of the injection to the nearest clock hour
  - complications, if any

#### **10.4.2 Case Report Form Completion**

The investigator is responsible for ensuring that data are properly recorded on each patient's CRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the CRFs (as indicated in the CRFs) to ensure that the observations and findings are recorded on the CRFs correctly and completely. The CRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan.

### **10.4.3 Study Summary**

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

### **10.4.4 Retention of Documentation**

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of CRFs should be maintained on file.

For countries falling within the scope of the ICH guidelines, the Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

## **10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments**

### **10.5.1 Labeling/Packaging**

Study medication will be packaged, labeled, and supplied by Allergan. The assembled Brimo DDS Applicator System is individually packaged in foil pouches with desiccant and sealed. The entire foil pouch package is sterilized. Each foil pouch is packaged in a carton with a single-panel label and a unique identifier. The medication will be identified as containing an investigational compound or Sham.

### **10.5.2 Clinical Supply Inventory**

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the patients, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator.

### **10.5.3 Return or Disposal of Study Medications/Treatments**

All used applicators shall be disposed of on-site by unmasked site personnel, using a standard syringe sharps container, and destroyed according to the site's sharps disposal procedures.

All unused investigational product kits, attributed or not attributed to patients, and malfunctioning applicators shall be returned to a third party contractor as designated by Allergan. See the Procedure Manual for details.

### **10.6 Monitoring by the Sponsor**

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

### **10.7 Handling of Biological Specimens**

Samples of blood and urine for evaluation of hematology, chemistries, and urinalysis will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology [CAP] or Clinical Laboratory Improvement Amendments [CLIA] certification).

Blood samples obtained at selected sites will be analyzed for AGN-190342 by an Allergan-designated laboratory using a validated method. This laboratory will meet Good Laboratory Practice requirements.



Blood samples obtained for genotyping and gene expression analysis will be sent to the central laboratory for storage until the samples can be sent to the Institute of Human Genetics at the University of Regensburg for analysis using a validated method. This laboratory meets Good Laboratory Practice requirements.

Details about the handling, processing, and shipment of all biological specimens are provided in the Procedure Manual.

All samples will be destroyed by Allergan or Allergan designee. Allergan shall have full ownership rights to any biological specimens/samples derived from the study.

## **10.8 Publications**

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

## **10.9 Coordinating Investigator**

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

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## 12.2 Protocol Amendment Summary Amendment 1

Title: Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

Protocol 190342-038 Amendment 1

Date of Amendment: March 2014

### Amendment Summary

This summary includes changes made to Protocol 190342-038 (approved August 2013).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Investigator Signature Page	Updated text and removed all but 1 investigator signature space	To make consistent with current version of protocol template
Summary	Revised wording for BCVA entry criteria Deleted (mm <sup>2</sup> ) following lesion area for primary efficacy variable	For clarification
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 4.5.3	Added roflumilast as prohibited medication	Roflumilast would have confounding effect on the study
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 23-May-2017

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 7.3.1	Added data transformation for primary efficacy analysis	For clarification
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 10.7	Added name of new laboratory	A different laboratory will analyze pharmacokinetic samples
Section 11	Added references for gene expression analysis	To support Section 6.4.10.3

Approval Date: 23-May-2017

### 12.3 Protocol Amendment Summary Amendment 2

Title: Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

Protocol 190342-038 Amendment 2

Date of Amendment: August 2014

#### Amendment Summary

This summary includes changes made to Protocol 190342-038 Amendment 1 (March 2014).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Summary; Sections 2.1, 3, 4.3, 6.1.2, 6.4.1, 6.4, and 7.2.2	Updated scotopic microperimetry to be scotopic/mesopic microperimetry	Patients will use one of 3 neutral density filters (0, 1.0, 2.0) with the Nidek MP-1S microperimetry instrument; this filter is selected based on the filter section test. Use of the 0 density filter is considered mesopic whereas the use of the 1.0 or 2.0 neutral density filters are considered scotopic.
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]

Approval Date: 23-May-2017

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Summary; Sections 6.4.10.4, 7.3.4, 8.3.1, 8.3.3 to 8.3.14, and 10.4.1	Updated complete ophthalmic examinations to include: external examination of the eye and adnexa, screening for eyelid/pupil responsiveness, slit-lamp biomicroscopy, indirect ophthalmoscopy, dilated fundus examination, and IOP	For clarification and consistency, to include all components of the ophthalmic exam in each section
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Table 1; [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 23-May-2017

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	Included information about study technicians not performing fundus photography and not being present during implant assessments, implant photography, or post-injection assessments	For clarification
[REDACTED]	[REDACTED]	[REDACTED]
Section 6.4.2	Added: “Individuals performing the BCVA measurements will be certified by an Allergan representative or third-party vendor if they have not been certified within the previous 12 months or have not performed at least 2 standard ETDRS manifest protocol refractions and 2 standard ETDRS visual acuity assessments within the previous 12 months.”	Clarification of BCVA certification requirements
Section 6.4.4	Added italicized text: “The reproducibility of the mean retinal sensitivity threshold measurements from the repeat assessment performed during the Screening Visit 2 will be used to confirm patient eligibility <i>by the CRC.</i> ”	The results from mean retinal sensitivity threshold eligibility assessments are to be assessed by the CRC to confirm the patients’ eligibility.
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 23-May-2017

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Section 8.8	Added text: “Study treatment will be discontinued in patients who develop neovascular AMD or any retinal disorder that prevents retinal visualization and quantification of the area of atrophic lesions or causes a sustained $\geq 30$ letter loss of BCVA; a sustained loss is defined as a loss evident on 2 consecutive study visits.”  Also added rationale for these criteria.	Clarification of criteria to define discontinuation of study treatment
Section 10.5.3	Revision of text describing return and disposal of study medications	For clarification
Section 11	Added new references	Added new references that were cited in Section 1

## 12.4 Protocol Amendment Summary Amendment 3

Title: Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

Protocol 190342-038 Amendment 3

Date of Amendment: September 2014

### Amendment Summary

This summary includes changes made to Protocol 190342-038 Amendment 2 (August 2014).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 23-May-2017

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Table 1, 6.4.6	Added row in Table 1 to clarify visit schedule for Fundus Autofluorescence (3-field) and Quantitative Fundus Autofluorescence (central field) Revised verbiage in section 6.4.6	For clarity
[REDACTED]	[REDACTED]	[REDACTED]
4.1	Revised number of sites from approximately 15 to 20 to approximately 15 to 30	To facilitate patient recruitment
Figure 2	Deleted figure	Deleted as this figure is no longer relevant with adjusted entry criteria

Approval Date: 23-May-2017



## 12.5 Protocol Amendment Summary Amendment 4

Title: Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

Protocol 190342-038 Amendment 4

Date of Amendment: October 2014

### Amendment Summary

This summary includes changes made to Protocol 190342-038 Amendment 3 (September 2014).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 23-May-2017

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Section 1	Changed lesions in which the total lesion area is greater than “12.5 mm <sup>2</sup> ” to “18 mm <sup>2</sup> ”	Correction
Section 5.9	Added text “The Sham treatment is administered using a needleless DDS Applicator. Refer to the Procedure Manual for the detailed instructions.”	Added for completeness
Section 6.4.2	Removed specific instructions on Standard and Low Luminance BCVA certification process	Simplification
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

## 12.6 Protocol Amendment Summary Amendment 5

Title: Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

Protocol 190342-038 Amendment 5

Date of Amendment: January 2015

### Amendment Summary

This summary includes changes made to Protocol 190342-038 Amendment 4 (October 2014).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Summary	Removed “loss of retinal sensitivity” from clinical hypotheses	Change in retinal sensitivity is an exploratory assessment.
Summary, Table 1, Sections 4.3, 6.4.4, 8.2, 8.3.3, 8.3.7, 8.3.9, 8.3.11, 8.3.13, and 8.3.14	Microperimetry will be conducted only at selected sites in patients who qualify and consent to the procedure	To ease patient recruitment
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Summary, Sections 2.1, 6.1.2, 6.1.3, 7.2.2, and 7.3.2	Changes in retinal sensitivity moved to an “Other” endpoint rather than a “Secondary” endpoint	Change in retinal sensitivity is an exploratory assessment

Approval Date: 23-May-2017

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Summary, Sections 7 and 7.6	Addition of possible interim analysis with first 50% of patients completing Month 18	To facilitate earlier project planning
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 5.3	Added “Corneal curvature, indocyanine green angiography (ICG), fluorescein Angiography (FA), and drug accountability may be performed by either masked or unmasked personnel.”	Clarification of masking procedures

Approval Date: 23-May-2017

## 12.7 Protocol Amendment Summary Amendment 6

Title: Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

Protocol 190342-038 Amendment 6

Date of Amendment: May 2015


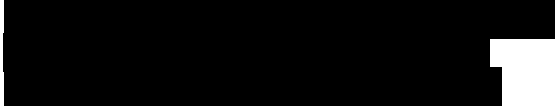
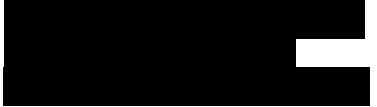
### Amendment Summary

This summary includes changes made to Protocol 190342-038 Amendment 5 (January 2015).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Summary, Section 4.3	Inclusion criterion changed: the study eye must have BCVA better than or equal to 45 letters (20/125 Snellen equivalent) rather than 55 letters (20/80 Snellen equivalent).	To facilitate patient recruitment
[REDACTED]	[REDACTED]	[REDACTED]
Section 4.1	Increased the number of sites from approximately 30 to approximately 40.	To facilitate patient recruitment
Table 2	Clarified footnote “b” to indicate that additional assessments beyond those listed in the table may be performed at the investigator’s discretion.	Clarification
[REDACTED]	[REDACTED]	[REDACTED]

Approval Date: 23-May-2017

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
		
Section 10.7	Removed the name of the specific laboratory used for blood sample analyses.	To prevent deviation if a different laboratory is chosen

Approval Date: 23-May-2017

## 12.8 Protocol Amendment Summary Amendment 7

Title: Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

Protocol 190342-038 Amendment 7

Date of Amendment: May 2017

### Amendment Summary

This summary includes changes made to Protocol 190342-038 Amendment 6 (May 2015).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Title page [REDACTED]	Updated contact information [REDACTED]	Provided updated information [REDACTED]
Summary, Sections 7.3.1 and 7.3.2	Revised primary efficacy analysis method from ANCOVA to MMRM	Changed to a method with greater statistical power
Summary, Sections 7, 7.6	Removed interim analysis when 100% of patients completed Month 18 and thus reduced number of database locks from 4 to 3	Management decision to perform the Month 18 analysis with 50% of patients made the later analysis unnecessary.
Table 1, Sections 6.4.5 and 8.3 [REDACTED]	Changed near-IR measurement from 7-field to 3-field [REDACTED]	Sufficient data can be collected with 3-field method [REDACTED]
Section 1	Added reference for cytoprotective effects of brimonidine	Additional data available
Section 1	Changed terminology from Brimonidine tartrate DDS to Brimonidine DDS Generation 1 and from Brimonidine free-base DDS to Brimonidine DDS Generation 2	For clarity and consistency with the investigator's brochure
Section 1	Changed concentration for Generation 1 from 200 and 400 µg to 132 and 264 µg	To better reflect the amount of active ingredient
Section 1	Changed percentage increase in brimonidine drug load from 30% to 50%, changing from tartrate to free base	Corrected error

Approval Date: 23-May-2017

<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Section 4.5.1	Added information on timing of YAG capsulotomy and cataract surgery and instructions regarding retinal tear and choroidal neovascularization in the fellow eye	Provided additional information to address frequent questions on these topics
Section 5.3	Added description of masking and unmasking at the sponsor after the interim analysis and clarified that the assessing investigator is masked	To show data integrity after the interim analysis
Table 2	Clarified that further monitoring should be for new intraocular pathology	Clarification
Sections 6.1.1, 6.1.2, 6.1.3, 7.2.1, 7.2.2	Added that efficacy measures and analyses refer to the study eye	Clarification
Section 6.4.1	Added standard and quantitative to FAF measurements	Clarification
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 7.1	For the mITT population, specified that analyses will be performed based on the randomized treatment	Changed to match standard sponsor definition
[REDACTED]	[REDACTED]	[REDACTED]
Section 7.2	Removed LOCF analyses	No longer needed because of change to primary analysis method
Section 7.3.4	Changed terminology from AEs of special interest to the primary safety measures outlined in Section 6.3	Clarification
Section 8.7	Moved text requiring that patients who develop neovascular AMD or concomitant retinal disorder in the study eye be discontinued from Section 8.8, required discontinuation from the study rather than just from treatment, and stipulated that discontinuation for a concomitant retinal disorder only applies to the study eye	Patients who develop concomitant retinal disease (as defined) are to be exited from the study in order to limit analysis to mITT population patients with GA secondary to AMD



<b>Section</b>	<b>Revision</b>	<b>Rationale</b>
Section 8.8	Removed language about treatment failures and deleted section; added new section 8.7.1 to provide rationale for not discontinuing patients due to treatment failure	Potential for bias as more sham patients may be removed for treatment failure; hurts potential to realize a treatment difference between sham and Brimo DDS; there are no available treatments to which patients can escape
Section 10.4.1	Removed references to printouts for source documents	Only electronic versions are needed
Section 11	Updated reference list	To align with changes in Section 1

